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Original Research

The relationship between inflammation and hematological parameters in chronic kidney disease

Chronic kidney disease and neutrophil lymphocyte ratio

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Abstract

Aim: The progression of Chronic Kidney Disease (CKD) is closely related to systemic inflammation and oxidative stress. This situation causes malnutrition, atherosclerosis, coronary artery calcification, heart failure, anemia, mineral and bone disorders, increasing mortality and morbidity. An increased number of leukocytes and their subtypes is a feature of the inflammatory process. The neutrophil- lymphocyte ratio (NLR), derived from leukocyte counts has been shown to be a strong indicator of acute and chronic inflammation, associated with cardiovascular risk. In our study, it was aimed to investigate the relationship between hematological parameters and Glomerular Filtration Rate (GFR) and proteinuria, which is an indicator of inflammation, in patients with CKD stage 3-5 without dialysis treatment.

Material and Methods: In the study, patient files were analyzed retrospectively. Patients with diabetes mellitus, active infection, malignancy, obesity, taking lipid and uric acid-lowering drugs, taking thyroid hormone replacement, and uncontrolled hypertension were not included in the study. A total of 178 patients (96 (53.9%) females, 82 (46.1%) males) and 20 healthy controls (12 (60%) females and 8 (40%) males) were included in the study. Patients were compared with the control group in terms of CKD stages, median values of hematological parameters and proteinuria status.

Results: A significant difference was found between the patient group and the control group in the neutrophil-lymphocyte ratio (NLR) and lymphocyte- monocyte ratio (LMO). While the GFR and albumin values were significantly lower in patients with proteinuria, the NLR values were found to be significantly higher. Correlation analysis revealed a positive correlation between the NLR value and proteinuria and ferritin, and a negative correlation with GFR and albumin.

Discussion: NLR, which is an easily applicable and inexpensive method, can be used as an indicator of proteinuria and inflammation in predialysis CKD. Although it seems to be usable in other hematological parameters, comprehensive studies are needed.

Keywords

Hemogram; Inflammation; CKD; Proteinuria

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Introduction

Chronic Kidney Disease (CKD) is a global public health problem with significant mortality and morbidity. The progression of CKD is closely related to systemic inflammation and oxidative stress. This condition causes malnutrition, atherosclerosis, coronary artery calcification, heart failure, anemia, mineral and bone impairment, increasing mortality and morbidity [1]. Inflammation is a complex biological response of vascular tissue to injury, infection, ischemia, and autoimmune diseases. In physiological conditions, the inflammatory response provides removal of the cause and initiates the healing process. Various cytokines and acute phase proteins are released to increase or decrease the inflammatory response. As a result, levels of positive acute phase reactants such as C-reactive protein (CRP) increase, while levels of negative acute phase reactants such as albumin decrease [2]. While this continuous inflammation seen in CKD is inversely proportional to kidney function, it is positively proportional to the amount of proteinuria. Studies have shown that inflammation is more common in cases of lower kidney function and higher proteinuria with an increased cardiovascular risk [3,4]. An increased number of leukocytes and their subtypes is a feature of an inflammatory process. The neutrophil- lymphocyte ratio (NLR), derived from the leukocyte count, has been shown to be a strong indicator of acute and chronic inflammation and is associated with cardiovascular risk [5]. Likewise, the platelet lymphocyte ratio (PLR) has been shown to be associated with significant cardiovascular outcomes [6]. Again, in a meta-analysis, it was stated that high NLR in patients with CKD was associated with all-cause and cardiovascular mortality [7]. In our study, in the light of all these data, it was aimed to investigate the relationship between hematological parameters and Glomerular Filtration Rate (GFR) and proteinuria, which is an indicator of inflammation, in patients with stage 3-5 CKD who did not receive dialysis treatment.

Material and Methods

The files of patients who applied to the Nephrology Policlinic were retrospectively analyzed. Patients over 18 years of age with a diagnosis of CKD were included in the study. Patients with diabetes mellitus, active infection, malignancy, obesity, taking lipid and uric acid-lowering drugs, taking thyroid hormone replacement, and uncontrolled hypertension were not included in the study. As a control group, healthy volunteers who do not have any known illnesses, and who do not use regular medication and do not use alcohol or smoking were included. Patients' demographic data such as age, gender, chronic diseases, medications used, body mass indexes (BMI) were scanned from the follow-up files of the patients.

Biochemical Analysis:

Complete blood count (hemogram), blood urea nitrogen (BUN, mg / dL), creatinine (mg / dL), sodium (Na, mmol / L), potassium (K, mmol / L) taken during routine outpatient clinic controls, calcium (Ca, mg / dL), phosphorus (P, mg / dL), magnesium (Mg, mg / dL), uric acid (mg / dL), albumin (g / dL), total protein (gr / dL), total cholesterol (mg / dL), triglyceride (TG, mg / dL), low density lipoprotein (LDL, mg / dL), high density lipoprotein (HDL, mg / dL), CRP (mg / L), ferritin (ng / mL), free triiodothyronine (FT3, pg / mL), free thyroxine (FT4, ng / dL) and thyroid stimulating hormone (TSH, μIU / mL), 25 OH vitamin D (ng / mL) and parathyroid hormone (PTH, pg / mL) values were recorded. Protein excretion of the patients was calculated by dividing the total amount of protein in the spot urine by the amount of creatinine. GFR was calculated using the MDRD formula (MDRD formula = 170 x (serum Cr) -0.999 x (age) -0.176 x (0.762 if patients are female) x (1.180 if patients are black) x (serum BUN) -0.170 x [(Albumin) + 0.318]). NLR, absolute neutrophil count divided by lymphocyte count, PLR, platelet number divided by lymphocyte number, neutrophil to monocyte ratio (NMR), neutrophil count divided by monocyte and lymphocyte to monocyte ratio (LMR) was calculated by dividing the lymphocyte count by the monocyte count. The necessary ethics committee approval was obtained for the study (Erzurum BEAH KAEK Decision No: 2021 / 04-69).

Statistical analysis:

The data were evaluated using the IBM SPSS Statistics 22 program. The compliance of the variables to normal distribution was examined by visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyzes were performed using means and standard deviations for normally distributed variables. While analyzing the data, independent groups t- test (Student's t-test) was used to compare two groups, and the Mann-Whitney U test was used if the conditions were not met. With one-way analysis of variance and Tukey HSD test, one of the multiple comparison tests, for comparing three or more groups, when the conditions were not met, the Kruskal-Wallis and Bonferroni-Dunn test from multiple comparison tests were used. Chi-square and Fisher Exact's test methods were used in the analysis of categorical data. A p-value less than 0.05 was considered statistically significant. Receiver Operating System (ROC) curve analysis was performed for diagnostic decision-making features. The existence of significant limit values, sensitivity and specificity values of these values were calculated. Then, a logistic regression analysis of these cut-off values was performed.

Results

A total of 178 patients (96 (53.9%) females, 82 (46.1%) males) and 20 healthy controls (12 (60%) females, 8 (40%) males) were included in the study. The mean age of the patient group was 59.2 ± 14.3 years, and the mean age of the control group was 36 ± 9.4 ($p < 0.001$) years. While the NLR value was found to be statistically significantly higher in the patient group, the LMR value was found to be significantly lower ($p < 0.001$, $p < 0.001$). There was no significant difference between PLR and NMR. The Stage-3 CKD group and control group were compared. The mean age of the patient group was 60 ± 14.9 years, which is significantly higher than the average age of the control group ($p < 0.001$). Uric acid, CRP, triglyceride and NLR levels of the patient group were found to be significantly higher, and albumin, LMR and FT3 levels were found to be significantly lower ($p < 0.001$).

The patients were then compared with each other according to their stages. There was no significant difference between the ages of the patients ($p = 0.293$). As the stage of the patients increased, albumin, hemoglobin, 25-OH vitamin D and

Table 1. Comparison of demographic and laboratory data according to the stages of the CKD

	Stage 3 (n=74)	Stage 4 (n=62)	Stage 5 (n=42)	p
Age (years)	60±14.9	56.5±13.3	62±14.6	0.293
GFR (ml/min)	39.2±7.1	21.2±4.2	9.5±3.5	<0.001
Uric Acid (mg/dL)	6.6±1.4	6.2±1.6	6.4±1.5	0.502
Albumin (gr/dL)	4.2±0.4	4.2±0.3	3.8±0.5	0.001
Proteinuria (gr/day)	0.93±1.3	1.66±1.5	3.06±2.7	<0.001
Hemoglobin (gr/dL)	12.6±2	11.6±1.5	9.4±1.6	<0.001
NLR	2.81±1.1	2.96±1	4.06±1.5	0.003
PLR	129.9±52.2	140.1±66.9	180.7±108.7	0.165
NMR	9.1±3.1	9.7±3.2	10.2±4	0.609
LMR	3.4±1	3.5±1.3	2.96±1	0.119
MPV (fl)	10.4±0.9	11±1.1	10.5±1.1	0.094
CRP (mg/l)	3.1±2.2	4.8±4.7	3.6±4.8	0.262
Ferritin (ng/ml)	133.6±150.4	123±77.3	204.1±134	0.019
PTH (pg/ml)	84.5±56.7	152.9±107.3	397.7±353.6	<0.001
25-OH D (ng/ml)	22.1±9.4	19.6±12.9	13.7±7.7	0.002
FT3 (pg/ml)	2.59±0.5	2.62±0.9	2.16±0.6	0.009

GFR: Glomerular Filtration Rate, NLR: Neutrophil Lymphocyte Ratio, PLR: Platelet Lymphocyte Ratio, NMR: Neutrophil Monocyte Ratio, LMR: Lymphocyte Monocyte Ratio, MPV: Mean Platelet Volume, CRP: C-reactive protein, PTH: Parathormone

FT3 levels were found to be significantly lower. A significant difference was found between the NLR levels of Stage-3 and Stage-5 patients and Stage-4 and Stage-5 patients (p = 0.003, p = 0.019, respectively). However, no significant difference was found between the other parameters, PLR, NMR, LMR, MPV and CRP values. Comparison of patient data according to stages is given in Table1.

The median values of the hematological parameters of the patients were determined. The median value for NLR was 2.8, 129 for PLR, 9.1 for NMR, 3.1 for LMR and 10.5 for MPV. The patients were then compared according to these median values. While albumin and LMR values were significantly lower in patients with NLR values of 2.8 and above, proteinuria, ferritin, PLR and NMR values were found to be significantly higher. However, no significant difference was found in GFR and CRP values. NLR values were found to be significantly higher in patients with a PLR of 129 and above, while the albumin and MPV values were found to be significantly lower. NLR values and proteinuria levels were found to be significantly higher in patients with NMR value of 9.1 and above. The comparison of the patients according to the median values for hematological parameters is given in Table 2.

Patients were divided into two groups, with and without proteinuria and compared. While the GFR and albumin values of patients with proteinuria were found to be significantly lower, NLR values were found to be significantly higher. Comparative data are given in Table 3.

In correlation analysis with hematological parameters, positive correlation was found between NLR value and proteinuria (r= 0.242, p= 0.020) and ferritin, and negative correlation with GFR and albumin. There was a negative correlation between PLR value and albümin (r= -0.367, p < 0.001).

As a result of the ROC analysis performed for the diagnostic value of NLR in predicting proteinuria, this value was found to be 2.4 (AUC:0.906, 95% C.I. 0.838-0.974, Sensitivity 83%,

Table 2. Comparison of the patients according to the median value of NLR, PLR, NMR, LMR and MPV

	NLR < 2.8 (n=88)	Median NLR ≥ 2.8 (n=90)	p
GFR (ml/min)	27.9±12.5	24±13.9	0.127
Albumin (gr/dL)	4.2±0.4	4±0.4	0.015
Proteinuria (gr/day)	1.1±1.5	1.9±1.9	0.007
PLR	106.7±38.2	183.3±84.1	<0.001
NMR	8±2.3	11.1±3.5	<0.001
LMR	3.85±1.2	2.89±0.9	<0.001
Ferritin (ng/ml)	80.3±12.1	153.7±22.9	0.010
	PLR < 129 (n=92)	**PLR ≥ 129 (n=86)**	**p**
Albumin (gr/dL)	4.22±0.4	4±0.4	0.011
Age (years)	56.5±14.4	62.3±13.1	0.047
Hemoglobin (gr/dL)	12±2.1	11±2.0	0.008
Ferritin (ng/mL)	112.3±85.8	179.8±152.7	0.023
NLR	2.36±0.7	3.66±1.25	<0.001
NMR	8.7±2.9	10.2±3.7	0.027
LMR	3.79±1.1	2.97±1.0	0.001
MPV (fL)	10.85±1.0	10.35±1.0	0.027
	NMR < 9.1 (n=90)	**NMR ≥ 9.1 (n=88)**	**p**
NLR	2.52±0.9	3.53±1.28	<0.001
Uric Acid (mg/dL)	6.8±1.5	6.0±1.3	0.017
LMR	3.08±1.04	3.65±1.18	0.004
Proteinuria (gr/day)	1.05±1.5	1.79±1.81	0.007
	LMR < 3.1 (n=88)	**LMR ≥ 3.1 (n=90)**	**p**
Age (years)	63.2±13.4	55.8±13.7	0.006
Ferritin (ng/mL)	175.3±128.8	119.5±123.9	0.009
NLR	3.48±1.3	2.59±1.0	<0.001
PLR	177.9±83.9	111.5±42.7	<0.001
NMR	8.37±2.6	10.58±3.8	0.002
	MPV < 10.5 fl (n=79)	**MPV ≥ 10.5 fl (n=99)**	**p**
Uric Acid (mg/dL)	6.8±1.3	6.1±1.6	0.019
CRP (mg/L)	5.25±4.3	3.85±4.7	0.017

GFR: Glomerular Filtration Rate, NLR: Neutrophil Lymphocyte Ratio, PLR: Platelet Lymphocyte Ratio, NMR: Neutrophil Monocyte Ratio, LMR: Lymphocyte Monocyte Ratio, MPV: Mean Platelet Volume, CRP: C-reactive protein

Table 3. Comparison of patients with and without proteinuria

	Proteinuria (+) (n=140)	Proteinuria (-) (n=38)	p
Age (years)	58.2±13.9	63.1±15.3	0.133
GFR (ml/min)	23.7±12.8	34.4±11.6	0.001
Albumin (gr/dL)	4.1±0.5	4.3±0.3	0.008
FT3 (pg/mL)	2.44±0.5	2.71±1	0.378
Uric Acid (mg/dL)	6.4±1.6	6.4±1.3	0.775
Ferritin (ng/mL)	149.5±130.1	135.6±123.7	0.685
PTH (pg/mL)	197.3±240.1	126.8±121.2	0.432
25-OH D (ng/mL)	19.1±11.4	20±8.5	0.360
Hemoglobin (gr/dL)	11.3±2.2	12.1±1.7	0.102
NLR	3.28±1.2	2.43±1.1	0.002
PLR	124.4±58.6	167.1±81.8	0.173
NMR	9.9±3.4	8.4±2.8	0.067
LMR	3.2±1.1	3.7±1.1	0.067
MPV (fL)	10.7±1.1	10.4±1	0.334
CRP (mg/L)	3.9±3.9	3.6±3.7	0.814

GFR: Glomerular Filtration Rate, NLR: Neutrophil Lymphocyte Ratio, PLR: Platelet Lymphocyte Ratio, NMR: Neutrophil Monocyte Ratio, LMR: Lymphocyte Monocyte Ratio, MPV: Mean Platelet Volume, CRP: C-reactive protein, PTH: Parathormone

Specificity 79%). In the subsequent logistic regression analysis, it was determined that NLR being 2.4 and above increased the probability of proteinuria 18 times (95% C.I. 5.110-64.284, O.R: 18.125, Wald: 20.119).

Discussion

The relationship between CKD and cardiovascular disease has been known for a long time. Current guidelines recommend that patients with CKD be considered at high cardiovascular risk [8]. Studies have shown that inflammation seen in the course of CKD has an important role in the progression of both cardiovascular disease and kidney disease [9,10]. The presence of proteinuria or albuminuria in urine has obvious clinical significance as an early indicator of underlying renal pathology, before a concrete decline in renal filtration function. In addition to its role as a marker for CKD risk, it is now widely accepted that proteinuria is an independent predictor of cardiovascular morbidity and mortality in different populations [11, 12]. The white cell count in peripheral blood is a well-known marker of systemic immunoinflammatory activity. In recent studies, NLR has been shown to be a powerful indicator in determining inflammation in cardiac and non-cardiac diseases. These studies confirm a strong association of NLR with the progression of end-stage renal failure (ESRD), especially in CKD patients. Therefore, monitoring proteinuria has an important role in CKD patients. While there are studies on NLR and CKD to date, information on the relationship between different peripheral leukocyte counts and proteinuria is limited. Studies generally include patients with DM [13,14]. In a study by Binnetoğlu et al., NLR was associated with the presence and degree of proteinuria in patients with stage 3 and 4 CKD [15]. In another study by Tatar et al., it was shown that NLR is an important parameter in predicting mortality in elderly patients with stage 3-5 CKD [16]. In another study of patients with CKD stage 1-3, similar to albuminuria and uric acid, NLR was shown to be a specific marker for patients with CKD Stage 3 [9]. In our study, NLR was found to be significantly higher in patients compared to the healthy control group. In addition, it was found that NLR levels increased with proteinuria in the stage 5 CKD group, in other words, NLR levels increased with CKD progression. In addition, when the patients were evaluated according to the presence of proteinuria, the NLR was found to be significantly higher in patients with proteinuria, while a negative correlation was found between NLR and GFR and albumin, and a positive correlation between proteinuria. The cut-off value for predicting proteinuria for NLR was found to be 2.4 and above. When the NLR is 2.4 and above, the probability of proteinuria increases at least 18 times, which is an important result.

Platelets play an important role in the pathogenesis of atherosclerosis, thrombosis and inflammation. It has been shown that PLR obtained from platelet count is a prognostic factor in some diseases, such as cardiovascular diseases and malignancies, and is associated with mortality [16-18]. Various studies have been conducted in various patient groups on PLR in CKD. In a study by Chen et al. on 70 patients with peritoneal dialysis (PD), it was shown that PLR is associated with cardiovascular events and that high PLR levels can predict the risk of cardiovascular events in these patients [19]. In a study by Turkmen et al., they showed that PLR can predict inflammation better than NLR in 62 patients with ESRD [20]. In a meta-analysis published by Valga et al., it was stated that PLR is associated with erythropoietin resistance and may be a better marker of inflammation than NLR in Stage-5 CKD population [21]. However, in our study, no significant difference was found between the patients in terms of either GFR values or the presence of proteinuria in PLR. Only a negative correlation was found between PLR value and albumin. Our results are not compatible with the literature may be due to the low number of our patients, but also suggest that NLR may be a more sensitive inflammation marker than PLR.

There are some publications showing that LMR and NMR values can be used as a prognostic factor in various inflammatory conditions and malignancies [22, 23]. Our study examined the relationship of these values with GFR and proteinuria. In terms of NMR values, there was no significant difference between the patient and control groups and between patients according to the stages. LMR value was found to be significantly higher in the control group compared to both the patient group and the stage-3 CKD group. However, in the comparison of these values according to the median values, significant differences detected for both proteinuria and uric acid suggest that these parameters should be studied. The strength of our study is that it has been comprehensively examined not only for NLR but also for other hematological parameters, with GFR and proteinuria as well as other parameters. However, the fact that diabetic patients were not included, and the number of our patients was relatively small, restricts our study to some extent.

As a result, our study has shown that NLR, which is an easily available and inexpensive method, can be used as an indicator of proteinuria and inflammation in predialysis CKD patients. Although it seems to be usable in other hematological parameters, comprehensive studies are needed.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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